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LETTER TO THE EDITOR

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Case of X-linked hypohidrotic ectodermal dysplasia, along with facial bilateral reticular pigmentation

Dear Editor,

We encountered a patient with X-linked hypohidrotic ectodermal dysplasia (XLHED) along with facial bilateral reticular pigmentation.

Since birth, a 17-year-old male had been experiencing fever caused by an increase in the outside temperature. Physical examination revealed severe dry skin over his entire body, scarce scalp hair, sparse eyebrows, normal nails, and only ten permanent teeth, mild saddle nose, thick lips, along with severe itchy xerotic dermatitis. Moreover, from his childhood, periorbital reticular pigmentation gradually spread bilaterally to eyebrows, cheeks, and jaw (Figure 1A). Skin biopsy revealed the absence of sweat glands (Figure 1B), and a 15-minute sweat test (41°C, 22% humidity) elicited no sweating (Figure 1C). Based on the clinical and histological phenotype, he was diagnosed with sporadic XLHED.

X-linked hypohidrotic ectodermal dysplasia, which is characterized by disorders of various organs including skin, is attributable to the abnormal development of the primordial external germ layer. Following are the four disease-causing genes that have been identified: (a) *EDA*, which accounts for X-linked forms, (b) *EDAR*, (c) *EDARADD*, and (d) *WNT10A*.[1] Genetic analysis using DNA extracted from peripheral blood cells revealed a novel single base c.1036T>C substitution in exon 9 of the ectodysplasin A gene (*EDA*), which causes a single p.C346R amino acid substitution. The gene mutation c.1036T>C has not been mentioned in 1000 Genome database. Furthermore, according to the software used for the structural analysis, the *EDA* mutation p.C346R is strongly predicted to cause major structural changes in the protein (Figure 1D,E).

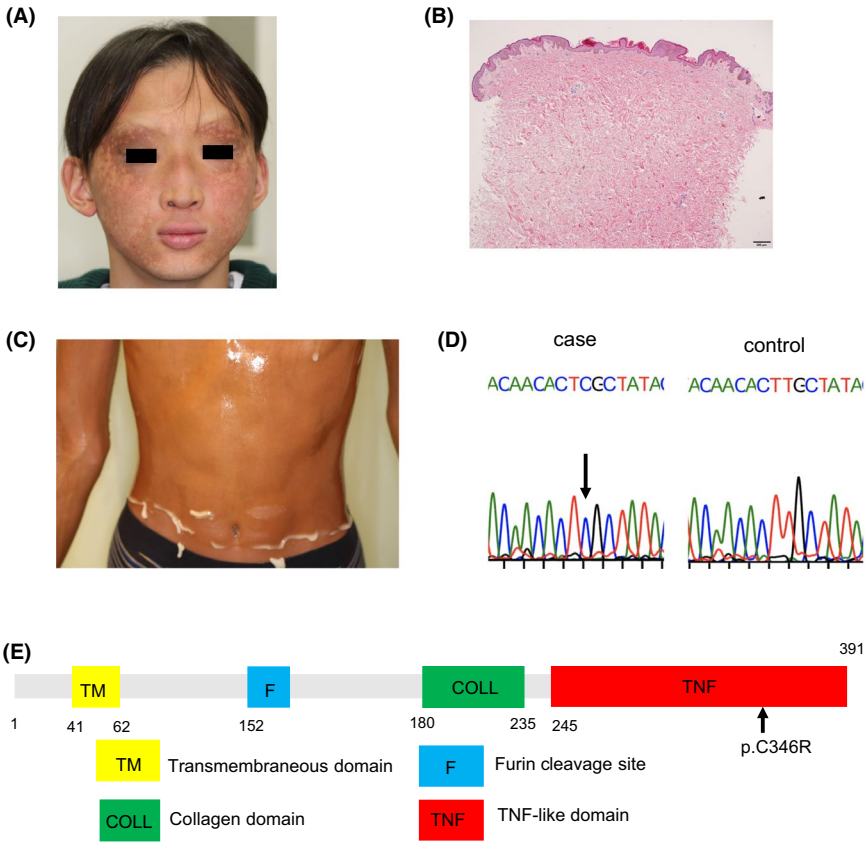

FIGURE 1 Clinical Appearance, Laboratory Findings, and Gene Mutation of the Patient. A, Clinical appearance of the patient. Facial bilateral reticular pigmentation was observed. B, Histopathological findings of the patient. H-E stain shows no sweat glands. C, No sweating was shown after a 15-min sweat test. D, A single base substitution was found in exon 9 of the ectodysplasin A gene (*EDA*). E, EDA and the mutation. The mutation p.C346R was structurally predicted to cause "probably damaging (score 1)" by in silico pathogenicity prediction tool, PolyPhen2

Atopic dermatitis (AD)-like eczema is a complication in 58.9% of patients with XLHED.[2,3] To confirm whether his severe xerotic dermatitis is caused only by the EDA gene, sequencing analysis was further performed for the filaggrin (*FLG*) gene. *FLG* mutations that are common in Japanese individuals were sequenced, as previously reported.[4] No mutation was found in the region we examined in *FLG* gene, suggesting mutation of EDA gene but not that of *FLG* seemed to be responsible for his atopic symptoms.

In the present case, facial bilateral reticular pigmentation was observed. To date, very few studies have reported facial pigmentation in ED patients. Namiki et al[5] reported a case of homogeneous, not reticular periorbital pigmentation, but genetic analysis was not performed in their report. Because facial bilateral reticular pigmentation has not been noted in patients with AD, this phenotype may be specific for XLHED patients.[3]

In conclusion, a novel phenotype of facial bilateral reticular pigmentation was found in a patient with XLHED, along with an *EDA* novel mutation p.C346R. Furthermore, mutation of EDA gene is considered to be responsible for severe xerotic eczema. An accumulation of cases of this sort and further studies on the genotype-phenotype correlation is necessary.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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